

Exhibit A

From: Heitkemper, Douglas T <Douglas.Heitkemper@fda.hhs.gov>
Sent: Wednesday, January 14, 2015 6:01 PM
To: Klontz, Karl C <Karl.Klontz@fda.hhs.gov>
Cc: Gratz, Samuel <Samuel.Gratz@fda.hhs.gov>
Subject: RE: possible response to reviewer...

Karl,

The statement, "FDA's Forensic Chemistry Center analyzed eighteen (18) different samples of OxyElite ProTM associated with Hawaii case-patients" is accurate. However, to be clear, multiple samples were obtained from a few of those patients. As far as I can tell, the 18 samples were associated with 13 actual case patients. However you want to respond is fine with me. I just wanted to make sure it was clear to you.

Response to comment, The terms "...drugs, poisons, pharmaceuticals..." appear to be overlapping-what are their definitions in this context? For example does drugs mean illegal drugs?:

There is some overlap among the terms "drugs", "poisons", and "pharmaceuticals". The laboratory performed non-targeted screens using the techniques gas chromatography/mass spectrometry (GC-MS) and liquid chromatography/mass spectrometry (LC-MS). These GC-MS and LC-MS screens are designed to broadly screen for those classes of compounds. The term "drugs" is used to cover those compounds that are not legitimate active pharmaceutical ingredients and includes many controlled substances, designer drugs, and analogs of legitimate active pharmaceutical ingredients. Poisons would be considered toxic agents that do not fall into the categories of "drugs" or "pharmaceuticals."

I also have just a couple of minor suggestions for the paragraph in the manuscript about the analyses done. See below.

Laboratory Analysis

Samples of OxyELITEProTM obtained from patients and retail shelves were analyzed by FDA's Forensic Chemistry Center. Non-targeted liquid chromatography-mass spectrometry and gas chromatography-mass spectrometry demonstrated the presence of combinations of aegeline, higenamine, caffeine, and yohimbine, or, in some products, a trio of DMAA, caffeine, and yohimbine. The following agents were not detected via the non-targeted screens used nor by additional targeted methodologies ~~absent~~: drugs, poisons, pharmaceuticals, toxic metals, usnic acid, N-Nitroso-fenfluramine, pyrrolizidine alkaloids, aristocholic acid, and phenethylamines. The amount of aegeline, higenamine and yohimbine in the samples were measured using liquid chromatography. Quantification of aegeline ranged from 33.2 mg/capsule to 112.0 mg/capsule while the range of higenamine varied from 15.5 mg/capsule to 41.6 mg/capsule. Yohimbine quantification varied from 1.6 mg/capsule to 3.2 mg/capsule. Forensic examination of product labels showed them to be authentic.

One last item, I know that CFSAN has completed some tox testing on aegeline and higenamine. From what I understand, the results weren't all that exciting, but you might want to add this information to the manuscript. It shows that FDA followed up with tox testing.

Thanks for letting us take a look.

Doug

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From: Klontz, Karl C
Sent: Wednesday, January 14, 2015 1:21 PM
To: Heitkemper, Douglas T
Subject: possible response to reviewer...

Doug,

As you give thought to how to respond to the journal reviewer regarding his comment ("from how many patients were samples obtained, and were these patients involved in Ae reports? The terms "...drugs, poisons, pharmaceuticals..." appear to be overlapping-what are their definitions in this context? For example does drugs mean illegal drugs?"), here's a draft response I was thinking about sending.

Let me know if it works for you or whether you'd like to provide a different response.

FDA's Forensic Chemistry Center analyzed eighteen (18) different samples of OxyElite ProTM associated with Hawaii case-patients. The term "drugs" refers to illicit (illegal) drugs; "pharmaceuticals" to agents prescribed by a physician or over-the-counter agents; and "poisons" to toxic agents that do not fall into the categories of "drugs" or "pharmaceuticals." We added the qualifier, "illegal," to clarify the use of the term, "drugs."

Karl